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REVIEW ARTICLE

Bone graft substitutes in anterior cervical discectomy and fusion

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Abstract Anterior cervical discectomy with fusion is a common surgical procedure for patients suffering pain and/or neurological deficits and unresponsive to conservative management. For decades, autologous bone grafted from the iliac crest has been used as a substrate for cervical arthrodesis. However patient dissatisfaction with donor site morbidity has led to the search for alternative techniques. We present a literature review examining the progress of available grafting options as assessed in human clinical trials, considering allograft-based, synthetic, factor- and cell-based technologies.

Keywords Cervical · Discectomy · Spinal fusion · Bone graft · Anterior cervical discectomy and fusion

Introduction

Spondylosis is the most common cause of neural dysfunction in the cervical spine. The degenerative changes of ageing—typically herniated disc, osteophyte formation and hypertrophied ligament—may compress the cervical neuraxis to present symptomatically as neck pain, radiculopathy, myelopathy or radiculomyelopathy [105, 106]. Conservative management, such as anti-inflammatories or physical therapy, is the preferred and often only required intervention [105]. In unresponsive patients, surgery is indicated.

Cloward [26] and Robinson and Smith [75] first described anterior surgical approaches in the 1950s as a method of neural decompression (Fig. 1). Following discectomy, Cloward directly removed compressive structures and followed with fusion using a dowel-shaped graft [26]. Robinson and Smith fused the adjoining vertebrae using a horseshoe graft harvested from the iliac crest (IC), but left decompression to occur secondarily [75]. Other configurations have been described, including the Simmons and Bhalla keystone graft [87].

These anterior cervical discectomy with fusion (ACDF) techniques have been used for decades with high rates of success. The indications for anterior cervical fusion (ACF) have also expanded to include the treatment of cervical realignment, trauma and tumour [3]. In 1960, Bailey and Badgley (whom had performed the first ACF in 1952) described a fusion technique for patients with neoplasm and instability involving onlay strut grafts [7], a concept now utilised following corpectomy [105].

Unfortunately, the harvest of autogenous bone for ACDF is associated with both short- and long-term morbidity. Discectomy alone has been assessed and considered sufficient by many authors [28, 65, 79, 103], with spontaneous fusion in 70–80% of cases [45]. However discectomy alone disrupts normal cervical lordosis and physiological loading of the spine [90, 106], and has been associated with poorer long-term clinical outcomes compared to autograft fusion [97].

Many alternatives which circumvent donor site morbidity are available as fusion substrates for ACDF (Table 1). Currently however, none are definitively superior to autograft [45, 104–106]. This article reviews the progress of allograft-, synthetic- and factor/cell-based

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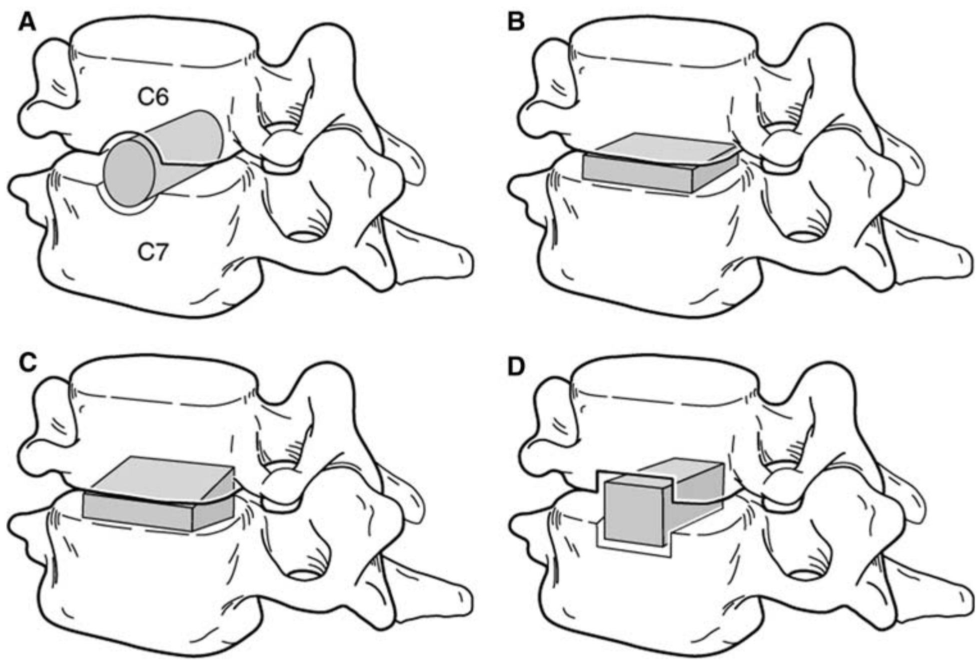

Fig. 1 Historical perspective of autogenous bone graft techniques. **a** Cloward dowel, **b** Smith-Robinson horseshoe, **c** Simmons-Bhalla keystone, **d** Bailey-Badgley onlay strut

Table 1 Summary of bone graft options in anterior cervical discectomy and fusion

Graft option	Fusion rates	Properties			Advantages	Disadvantages	Graft-associated complications	Implant cost[a]
		OG	OC	OI				
Autograft	74–100%	+	+	+	Host tissue	Limited availability, ↑ operating time and blood loss	DSM (up to ∼20%)	Nil
Allograft	54–100%	−	+	+/−	No DSM	Product variability, reliant on human bone banks, risk of infection, immunogenic	Graft collapse	++
Xenograft	0–100%	−	+	−	No DSM, unlimited supply	Risk of infection, immunogenic, fibrous host-graft interface	Reoperation	+
Ceramics	78–100%	−	+	−	No DSM, unlimited supply, biocompatible	Cage may be required	Graft dislocation and fracture	+
BOP	18%	−	+	−	No DSM, unlimited supply	Questionable biocompatibility, radiographic assessment difficult	Graft collapse and extrusion	+
PMMA	0–28% ST; 90% LT	−	+	−	No DSM, unlimited supply	Limited ossification	Graft migration	+
BMP	97–100%	−	−	++	No DSM, very effective adjuvant	Cost constraints, dosage/delivery not yet standardized	Neck swelling and dysphagia, ectopic bone formation, graft subsidence	+++
BMA	97%	+	−	+	Little DSM, abundant supply	Limited OG potential if used unadulterated	−	+/−
PRP	79%	−	+	OP	No DSM, abundant supply	Requires centrifugation, unknown efficacy	−	+/−

BMA bone marrow aspirate, *BMP* bone morphogenetic protein, *BOP* biocompatible osteoconductive polymer, *OC* osteoconduction, *DSM* donor site morbidity, *OG* osteogenesis, *OI* osteoinduction, *OP* osteopromotive—different from OI in that direct stimulation of bone formation is not a property, *PMMA* polymethylmethacrylate, *PRP* platelet rich plasma, *ST/LT* short/long-term

'+' and '−' indicates the relative applicability, with '+' yes, '−' no, and '+/−' being middle ground

[a] Costings are approximate and intended to be relative only

systems in human clinical studies for use in ACDF. The technologies of internal instrumentation, cages and arthroplasty are outside the scope of this review.

Graft principles

Graft incorporation occurs through the processes of hematoma formation, inflammation, vascularisation and creeping substitution [12, 19, 54]. Three ideal graft characteristics for successful fusion are osteogenesis, osteoinduction and osteoconduction [11, 54, 63]. These properties create new bone, stimulate osteoblastic differentiation of progenitor cells, and provide a scaffold for bone deposition, respectively. Only autograft possesses all of these features.

Complete fusion is aided by appropriate graft architecture [58, 91]. Cancellous bone, with its significant, interconnected porosity, enhances interface activity and bony ingrowth allowing greater entirety of bone repair. However, load-bearing capacity, for which a cortical architecture imparts greater structural integrity, is a particularly relevant consideration in the cervical spine.

While many studies define success using radiographic parameters, it is important to note that these do not necessarily correlate to clinical outcomes [59].

Autograft

Corticocancellous bone harvested from the iliac crest is widely used for the cervical spine [3]. A systematic review of the literature reported autograft to have a mean arthrodesis rate of 77% [106]. In one-level non-instrumented procedures, autograft fusion rates are a reported 83–99% [77, 108], but decreases with number of levels fused [37]. Autograft experiences relatively few incidences of graft complication, such as graft collapse or migration, and is biocompatible, poses no risk of disease transmission and is non-immunogenic [13]. For these reasons, autograft remains the standard of care for ACDF.

Unfortunately, the stipulation of a second surgical site not only increases operative time and blood loss but introduces significant donor site morbidity. Although the risk of harvest site morbidity has been suggested to be overstated [108], it is generally accepted within the literature to be of significant concern [77]. A retrospective study of one-level ACDF found 26.1% of patients suffered persistent pain and 15.7% experienced numbness at the harvest site [86]. Functional assessment revealed impairment in ambulation (12.7%) and other daily activities. Many other complications have been observed including infection, hematoma, bruising, pelvic fracture, periotoneal perforation, hernia, gait, ureteral injury, reoperation and poor cosmesis [81, 82]. Rawlinson reported 31% of patients felt donor site pain caused them to remain in hospital longer than if they had not had that procedure [72]. Finally, there are inherent limitations with supply and occasionally, autograft quality.

Some authors have investigated the harvest of autograft from alternative locations, such as the fibula [37], cervical vertebrae [60], clavicle [98], and the manubrium [69], so as to retain the advantages of autograft whilst circumventing its associated morbidity, to varying success. Others have explored the effectiveness of iliac crest reconstruction using synthetic materials in alleviating postoperative pain, with mixed results [16, 34, 73].

Allograft-based bone graft substitutes

Allograft bone is a commonly used alternative to autograft with a major advantage in avoidance of donor site morbidity, and also in supply, storage and reduced operating time [38]. The risk of disease transmission is a significant concern with the use of allograft [29]. Rigorous donor and serological screening and sterilization is employed to prevent bacterial and viral (human immunodeficiency virus, hepatitis viruses) infection, rendering risk of transmission remote [29]. The final properties of a particular allograft are significantly influenced by its method of preparation, which may vary widely between manufacturers. Unlike synthetic prosthesis, allograft substrates are additionally difficult to standardise given the heterogeneity of the donor population. Issues surround availability of the substrate, as bone banks are required and may be costly. Human allograft is available in two forms: mineralized and demineralized. Mineralized allograft is considered non-osteogenic, mildly osteoinductive, highly osteoconductive, and is available as fresh, frozen or freeze-dried preparations. Demineralized bone matrix is both osteoconductive and varyingly osteoinductive. Animal allografts are also available.

Mineralized allograft

Allograft is a comparable, albeit slightly inferior, alternative to autograft in ACDF with a mean arthrodesis rate of 74% [106]. Non-instrumented, single-level allograft fusion has been reported to result in a fusion rate of 94% even without the use of a postoperative collar [46]. However, a meta-analysis of four studies involving 310 patients undergoing one- and two-level ACDF concluded allograft was inferior to autograft in achieving radiographic fusion and suffered higher rates of graft subsidence [38]. In one-level non-instrumented procedures, Bishop et al. reported 87% allograft versus 97% autograft fusion rates (no statistical figure) [13]. In addition, studies have found allograft to be associated with higher incidence of kyphotic deformity [13] and delayed union [13, 92] compared to autograft. The correlation between pseudoarthrosis and collapse rates and increasing number of levels fused is more pronounced with allograft than autograft [20, 112]. Zdeblick and Ducker found that while autograft and IC allograft achieved 95% union for one-level fusion, only 38% allograft compared to 83% autograft fused for two-level procedures ($P = 0.03$) [112].

The recent use of anterior cervical plating has been suggested to increase arthrodesis rates and decrease subsidence, making allograft a more attractive option [30]. For instrumented one-level fusions, Samartzis et al. reported 100% arthrodesis with IC allograft compared to 90.3% in autograft, although this did not reach significance [77]. Schlosser et al. reported an average 94.5% arthrodesis rate for patients who underwent one- up to four-level plated fusions [80]. Kaiser et al. found higher fusion rates in ACDF with plating than non-plating for one- and two-level arthrodesis, from 522 patients using cortical allograft [47]. Long-term follow-up of patients receiving allograft with plating reported clinical and radiological success [111]. Although short-term costs of instrumented allograft compared to non-plating may be expensive, the postoperative period is shorter and 5-year cost-effectiveness similar [4].

Cortical bone harvested from cadaveric fibulae has been purported to provide enhanced mechanical support, at the expense of osteoconductivity, over IC substrate [30]. For non-instrumented ACDF using fibula allograft, Martin et al. achieved satisfactory fusion rates of 90% at one- and 72% at two-levels, with 5% graft subsidence. In one- and two-level instrumented ACDF, Suchomel et al. found no statistically significant difference for non-union ($P = 0.806$) or collapse ($P = 0.369$) between fibula allograft and IC autograft [92]. Dense cancellous allograft (DCA) with plating has also been investigated. Although good rates of fusion (82–96%) may be achieved due to superior porosity [8, 74], and lab-tested biomechanical stability appears equivalent to autograft [76], DCA demonstrates unacceptably high rates of resorption (53%) leading to graft voids [74]. Smoking status and poorer fusion rates, while bearing no significance in some studies [77, 92], have been established in others [13, 58], and appears to be more relevant in allograft than autograft procedures [2, 13].

Demineralized bone matrix (DBM)

DBM is the only allograft with osteoinductive properties, albeit at a highly variable rate. Unfortunately major concerns surround this high degree of product inconsistency and lack of product information [6]. A frequently cited article prospectively compared freeze-dried allograft augmented with DBM against autograft [2]. Clinical results were comparable. However, although no results reached statistical significance, there was a trend towards inferior outcomes in the allograft/DBM group in regards to fusion rates and graft collapse, especially evident in smokers. There was no allograft only group for which the exact impact of DBM could be extrapolated.

Animal allograft (Xenograft)

Bovine bone was first introduced by Maatz and Bauermeister in 1957 [55], two varieties of which are commercially available as Kiel bone or Surgibone. The medical literature regarding xenograft, which is solely osteoconductive, is incongruous. On the whole, clinical results appear to be satisfactory at least, with many authors presenting favourable data, albeit with varying accounts of complications [52, 57, 71, 78, 88, 94, 95]. Savolainen et al. compared xenograft with autograft in 250 cervical fusions and found no significant difference in fusion rates (both 98%) or angulation deformity between the two [78]. Siqueira et al. reported complete fusion in all 221 patients with no graft-related complications [88]. Espersen et al. reviewing 1,106 patients found that although equivalent functional results to autograft were achievable, xenograft was associated with increased reoperation rates, and so were ceased [35].

Xenograft induces a fibrous rather than bony union, however the clinical relevance of this is in contention. Ramani et al. noted a ‘halo’ appearance encaging the graft on imaging in all 65 patients on follow-up and interpreted this as fibrous tissue, but this had no clinical manifestation [71]. Similarly, Sutter et al. acknowledged the appearance of a halo, but concluded that it had no clinical significance with xenograft yielding comparable results to autograft in the literature [94]. Rawlinson confirmed the presence of connective tissue at the union site histologically, and also found inflammatory cells [72]. Surgibone contains 20–29% protein in the form of collagen which may be antigenic, despite manufacturer’s claims. Xie et al. recently conducted a histological study on a failed bovine union [109]. Despite apparent fusion on radiography, the authors could not attest to this histologically. Poor biocompatibility and the potential for viral transmission were noted.

Synthetic bone graft substitutes

Ceramics

Ceramics are crystalline structures of inorganic, non-metallic mineral salts produced at high temperatures.

Methodological variations in ceramic processing vary their final structural and chemical composition and hence their physiological properties [91]. Ceramics are attractive as graft substitutes in that they avoid donor site morbidity, demonstrate biocompatibility, present no risk of infection, and their supply is virtually limitless. The calcium phosphate ceramics tricalcium phosphate (TCP) and hydroxyapatite (HA) are the most widely investigated for use in the cervical spine. Because of their chemico-physical similarities to the bone mineralization phase [42], they provide an excellent osteoconductive scaffold for bone regeneration. Unfortunately, issues surround the appropriate resorbability and mechanical strength of these ceramics. TCP with a Ca:P molar ratio of 1.5 resorbs at too rapid a rate appropriate for the compressive requirements of the cervical spine. HA with a Ca:P ratio of 1.67 resorbs too slowly, shielding new bone from the mechanical stresses it requires to remodel [19]. Biphasic calcium phosphates, which combine 40% TCP with 60% HA, may yield a more physiological balance between mechanical support and bone resorption. Meanwhile, coral-derived HA produced through a replamineform process have been investigated.

Beta-tricalcium phosphate

Dai and Jiang recently published the only clinical controlled trial of β-TCP, contained in interbody cages, for patients with cervical radiculopathy or myelopathy [27]. A total of 62 patients were randomized into an anterior plating or non-plating treatment group, and followed for 2 years. While at 3 months non-plating showed a significantly slower fusion rate than plating ($P < 0.05$), at 6 months, successful fusion was noted in all patients. Although non-plating had issues with vertical cage migration ($P < 0.05$), both groups had equally significant improvements in clinical outcomes. The authors concluded interbody cage containing β-TCP to be an appropriate treatment for cervical fusion, whether supplemented with internal fixation or not.

Hydroxyapatite (HA)

Koyama and Handa pioneered the clinical use of HA in ACDF [50]. A handful of clinical studies involving ACDF have been performed since [21, 49, 83, 93]. Kim et al., using a 30% porous HA graft, found all implants had achieved fusion at 6–12 months, with good clinical results and no graft collapse [49]. However 3/70 cases encountered graft dislocation early on due to inappropriate sizing. In another study using HA but with plating, complete fusion occurred in 98% of one-level and 100% of two-level procedures [21]. This presents an interesting comparison to autograft or allograft procedures where increased levels correlated to increased pseudoarthrosis [37]. Slight graft collapse (3%), deterioration (19%) and fracture (3%) were observed, but did not affect clinical outcomes which were good or excellent in 91% of patients. Preoperative kyphosis was rectified in all cases, compared to the Kim et al. study where plating was not used and 4/10 patients retained the deformity. Suetsuna et al. retrospectively analysed the records of 36 patients, who received wide decompression and HA (40–45% porosity) sunk slightly into the vertebral body, for one-level herniated cervical discs [93]. Mean time since operation was 4.5 years. A total of 100% had probable (11%) or definite (89%) bone union, and no graft-related complications were observed. The authors concluded that this technique was a viable replacement for the Smith-Robinson.

Coralline hydroxyapatite

The hydrothermal conversion of coral skeleton (calcium carbonate) in the presence of a phosphate donor yields calcium hydroxyapatite (known as coralline HA) and removes all immunogenic protein [85]. The development of coralline HA was a case of serendipity involving three collaborators who recognised the similarity of some coral species to bone architecture. Two genera with interconnected porosity have been identified for production, commercially available as ProOsteon 200 (50% porosity) or 500 (65% porosity), according to their pore size in microns. These two products are likened to cortical or cancellous bone, respectively [85]. Due to the compressive loading in the cervical spine, ProOsteon 200 has been preferred for ACF. Wittenberg et al. found it to be as strong as corticocancellous graft from the iliac crest [107].

Thalgott et al. reviewed 26 patients who received ProOsteon 200 with rigid plating for ACF [96]. After a mean follow-up of 30 months, there were no graft complications and 100% of the grafts were incorporated, albeit at a slower rate than what could be expected with autograft. Agrillo et al. using granulated coralline HA within a carbon fiber cage demonstrated complete fusion in all 45 patients at 12 months with no complications, in one- or two-level procedures [1]. McConnell et al. compared ProOsteon 200 with autograft both with rigid plating in a prospective randomized trial [59]. At 24 months, both groups demonstrated significant clinical improvement and similar fusion rates (HA 78%, autograft 79%). However, HA performed poorly on radiography with increased graft fragmentation ($P = 0.001$), collapse ($P = 0.009$) and loss of sagittal alignment (not significant). They concluded ProOsteon 200 to be structurally inadequate for use in cervical interbody fusion.

Biphasic calcium phosphate (BCP)

Yamada et al. performed a histological study of β-TCP, HA and varying ratios of the two in order to identify which was the most conducive to osteoclastic activity, and hence bone remodelling [110]. After 2 days cell culture, evidence of resorption was noted for pure β-TCP and BCP with an HA/β-TCP ratio of 25/75, but not for BCP 75/25 or pure HA. Interestingly, BCP 25/75 resorbed more extensively than pure β-TCP, probably due to calcium inhibition of osteoclasts, and formed resorption lacunae similar to that on normal bone. This suggests BCP to be a more natural surface than either β-TCP or HA alone. Due to mechanical requirements, BCP 60/40 is used clinically [110].

Cho et al. compared BCP 60/40 (Triosite) with autograft IC both within polyetheretherketone (PEEK) cages for ACDF in a randomized controlled trial of 100 patients [25]. Triosite took significantly longer than autograft to achieve union ($P < 0.05$), however fusion was 100% in both groups at 6 months. Patients with Triosite had significantly shorter hospital stay ($P = 0.001$), while autograft patients experienced a donor site complication rate of 6%. There was no significant difference in clinical outcomes, consistent for one- to three-level procedures. The authors concluded that delayed fusion of BCP did not impede it from being an appropriate substitute in ACF.

Biocompatible osteoconductive polymer (BOP)

Despite initial promise of BOP regarding its safety, osteoconductivity, biocompatibility and biodegradability [53], enthusiasm for this substitute has died considerably. Although BOP has demonstrated clinical outcomes comparable to autograft, it was found to be associated with poor incorporation and biodegradation profiles [44, 56]. BOP performs poorly on radiographic evaluation with high rates of graft collapse, displacement and non-union, and as such its appropriateness even as a spacer is questionable [33, 40, 43, 44, 61].

Polymethylmethacrylate (PMMA)

Two prospective randomized trials found PMMA to have no detectable clinical advantage over discectomy only [9, 103] or autograft [9]. Radiologically, Bärlocher et al. found PMMA achieved no fusion in all 24 patients at 12 months [9]. Van den Bent et al. found PMMA induced fewer osseous unions than discectomy only ($P < 0.005$), experienced graft migration into adjacent vertebrae and was associated with sclerosis of surrounding bone [103]. Hamburger et al. investigated the clinical long-term significance of reduced osseous union in PMMA interbody fusions, and found 77.5% of 249 patients reported successful outcomes after a minimum 10-year follow-up [41]. However, fusion with PMMA has been reported to occur 15–20 years postoperatively in 90% of cases [17]. Necrosis of adjacent vertebrae and limited ventral ossification were also noted [17]. Some authors have investigated the modification of PMMA into a cage structure filled with autologous cancellous bone, reporting successful fusion rates with limited donor site morbidity [24, 67].

Factor- and cell-based approaches for bone graft substitutes

Emerging adjuvant therapies have allowed surgeons the option of composite bone grafts. The addition of an osteoinductive and/or osteogenic substance provides theoretical benefits when combined with an osteoconductive substrate. The most potent and promising of these adjuvants are the highly osteoinductive bone morphogenetic proteins, discovered by Urist in 1965 following his observation of bone growth from animal demineralized bone matrix [100]. Human BMPs may now be produced through recombinant techniques and produced on a large scale. Of interest in the cervical spine is the recombinant human BMP-2 (rhBMP-2) which has been the focus of a number of human clinical studies. Less expensive alternatives include bone marrow aspirate taken from the iliac crest and platelet rich plasma.

Bone morphogenetic protein (BMP)

BMPs have shown considerable promise in the human lumbar spine [15, 22] and in animal models [113] of anterior cervical fusion. Recently, a number of clinical studies have focused on its appropriateness in the human cervical spine, with consistently reported fusion rates of 100% [10, 14, 51, 84, 99, 101, 102]. Baskin et al. conducted the first prospective randomized controlled trial for anterior cervical interbody fusion, comparing rhBMP-2 with IC autograft, both placed within a fibula allograft and supplemented with anterior plating [10]. All 33 patients from both groups were fused by 6 months. At 24 months, the rhBMP-2 group had significantly better improvement in neck ($P < 0.03$) and arm ($P < 0.03$) pain than autograft, had no complications attributable to rhBMP, and had avoided statistically significant pain ($P < 0.007$) from the harvest site at 6 weeks. Boakye et al. in a retrospective review of 23 patients with one- to three-level procedures similarly found 1.05 mg/level of rhBMP-2 in PEEK cages induced solid fusion with good clinical outcomes and no significant morbidity [14]. However ectopic bone formation was observed to occur in three patients who were early on in the series and had received twice that amount.

However, many authors have elucidated the need for caution when using rhBMPs in the cervical area. Smucker et al. performed a multivariate analysis and found patients receiving rhBMP-2 to have a 10.1-fold increase in risk for swelling complication compared to those that did not receive rhBMP-2 [89]. In a retrospective review of 151 patients undergoing ACF using rhBMP-2 with plating, Shields et al. found 23.2% had suffered complications including hematoma, swelling, dysphagia, and increased hospital stay [84]. The authors noted their three-and-a-half-fold dose of BMP (2.1 mg BMP/level) compared to Baskin et al. (0.6 mg/level) as a possible reason, perhaps causing an excessive inflammatory response in the initial phase of bone healing. Tumialan et al. noted a decrease in dysphagia with a dosage reduction from 2.1 mg/level down to 0.7 mg/level, and from multilevel compared to single-level procedures [99]. In a prospective non-randomized study Buttermann compared BMP-2 with allograft against IC autograft in ACDF [23]. Using 0.9 mg BMP/level he found that although both groups demonstrated similar clinical improvements, 50% of the BMP group suffered dysphagia caused by neck swelling compared to 14% autograft.

In a letter, Dickerman et al. reported clinical success with a dose of 1.05 mg/level insulated by a DBM putty and delivered in PEEK cages, as these measures provide containment of the BMPs [32]. In a study that contained rhBMP-2 using thrombin glue and bioabsorbable spacers, no graft-related complications occurred [51]. Vaidya et al. reviewed the cases of 22 patients who received 1 mg rhBMP-2/level contained in PEEK cages and 24 patients who received allograft spacer with DBM [101]. BMP performed well radiographically with probable fusion in 100% of patients at 12 months. Allograft attained similar results. BMP had statistically significant dysphagia associated with anterior swelling, with severity observed to be dose-dependent. Compared to allograft, the BMP procedure was three times more expensive, and so was ceased [101]. In another study by the same lead author, rhBMP-2 with allograft for cervical fusion was ceased despite 100% fusion, due to a 33% incidence of graft subsidence [102].

Costs associated with the implementation of BMP for ACF may be prohibitive, however it remains to be seen how cost-effective they are compared to autograft and other alternatives long-term [23]. Further investigation is required in determining the optimal dose and delivery method of BMP for ACF, whether a measurable clinical advantage is produced, and if so, in whom these procedures should be performed.

Bone marrow aspirate (BMA)

BMA has been used as part of a composite graft in conjunction with an osteoconductive scaffold held within a mechanical structure for ACF [48, 68]. BM aspiration from the IC causes minimal morbidity while providing osteogenic potential [5]. Due to the scarcity of osteoprogenitor content, selective-retention or culture-expanded cell technology may be employed to maximise osteogenecity, although these add to costs [5, 66]. Khoueir et al. reported on the use of BMA soaked in collagen-hydroxyapatite matrix inside fibula allograft for instrumented multilevel ACF [48]. A total of 81.7% of patients demonstrated clinical improvement and 96.8% had radiographic fusion, with no graft-related complications. Several limitations of this study prevent direct comparison to autograft, however it does suggest BMA to be a safe, potentially efficacious and cheaper alternative to BMP.

Platelet rich plasma (PRP)

The supplementation of platelet concentrate in grafting is purported to benefit bone healing through provision of osteopromotive growth factors and an osteoconductive fibrin clot meshwork [5, 36]. Feiz-Erfan et al. conducted a double-blinded randomized trial for ACF using instrumented allograft with or without platelet-gel concentrate [36]. Platelet-gel showed no evidence of promoting early fusion and achieved no significant difference in arthrodesis rates at 12 months.

Conclusion

There are several acceptable and promising graft options for ACDF. Although many studies have investigated the effectiveness of these substrates (Table 2), currently, no option is conclusively superior to autograft. This is in part due to shortcomings in the literature. Firstly, many studies employed suboptimal study design, for example were small, retrospective, non-randomized or observer-biased. Secondly, discrepancy of predefined endpoints and non-standardised criteria for assessing radiographic fusion and clinical outcome creates heterogeneity of studies. Finally, the addition of plating following ACDF reported in a number of studies has subsequently been found to be significant in increasing fusion rates, regardless of number of levels fused [39, 62]. These inconsistencies make direct comparative analysis very difficult.

With this in mind, we tentatively draw the following conclusions:

1. *Autograft* remains the standard of care for ACDF, however patient dissatisfaction at the harvest site remains a significant drawback of this graft option [86].

Table 2 Summary of discussed studies

First Author	Year	Design	Graft (including controls)	Plate	Cage	Number of patients according to levels operated					Specified endpoint (range)	Fusion rate (%) according to level				Significant complications related to graft
						1	2	3	4	Total		1	2	3	4	
Autograft + allograft-based bone graft studies																
Autograft																
Wright	2007	Prospective	Autograft (IC)	No	No	54	43	–	–	97	12 months	89	79	–	–	DSM (2%)
Human allograft																
An	1995	Prospective, semi-random	Allograft + DBM	No	No	19	16	4	–	39	17.5 months (12–31)	52.6	62.5	25	–	None
			Autograft (IC)			19	17	2	–	38	19.4 months (12–33)	73.4	76.5	50	–	None
Balabhadra	2004	Retrospective	DCA	Yes	No	60	38	–	–	98	12 months	96 (1–2)		–	–	None
Bishop	1996	Prospective, semi-random	Allograft (IC)	No	No	32	14	3	–	49	31 months (3–43)	87	89 (2–3)		–	Graft collapse
			Autograft (IC)			60	20	3	–	83		97	100 (2–3)		–	DSM (10%)
Brown	1976	Retrospective	Allograft (IC)	No	No	32	19	2	–	53	20 weeks	94 (1–3)			–	Graft collapse in 2–3 level fusions
			Autograft (IC)			29	14	2	–	45		97 (1–3)			–	DSM
Fernyhough	1991	Retrospective	Allograft (F)	No	No	–	11	43	5	59	48 months (24–87)	–	82	57	30	Graft dislodgement
			Autograft (F)			–	6	49	12 (4–5)	67	83.3 months (24–131)	–	75	78	54 (4–5)	
Jagannathan	2008	Retrospective	Allograft (F)	No	No	170	–	–	–	196[a]	22 months (12–124)	94	–	–	–	↑ focal kyphosis in all patients
Kaiser	2002	Retrospective	Allograft (F)	Yes	No	157	76	–	–	251[a]	15.6 months (9–40)	96	91	–	–	None
			Allograft (F) control taken from Martin (1999) study							289						
Martin	1999	Retrospective	Allograft (F)	No	No	269	18	2	–	317[a]	33 months (24–51)	90	72	0	–	None
Rhee	2007	Retrospective	DCA	Yes	No	14	13	–	–	27	15 months (12–26)	82 (1–2)		–	–	Graft resorption
Samartzis	2005	Retrospective	Allograft (IC)	Yes	No	35	–	–	–	35	12 months (5–55)	100	–	–	–	None
			Autograft (IC)			31	–	–	–	31		90.3	–	–	–	None
Schlosser	2006	Retrospective	Allograft	Yes	No	80	57	53	29	219	76.5 months (56.1–134.4)	96	96.5	94	86	Reoperation for junctional disease (6%)
Suchomel	2004	Prospective semi-random	Allograft (F)	Yes	No	15	11	–	–	26	39.4 months (24–48)	93.3	93.5	–	–	None
			Autograft (IC)			30	23	–	–	53		100	90.9	–	–	None

Table 2 continued

First Author	Year	Design	Graft (including controls)	Plate	Cage	Number of patients according to levels operated					Specified endpoint (range)	Fusion rate (%) according to level				Significant complications related to graft
						1	2	3	4	Total		1	2	3	4	
Yue	2005	Retrospective	Allograft (F)	Yes	No	28	26	14	3	71	7.2 years (5.4–11.1)	92.6 (1–4)				Adjacent level degeneration
Zdeblick	1991	Prospective, semi-random	Allograft (IC)	No	No	19	8	–	–	27	12 months	95	38	–	–	Graft collapse
			Autograft (IC)			41	18	1	–	60		95	83		–	None
Xenograft																
Espersen	1984	Retrospective	Xenograft	No	No	NS	NS	NS	NS	NS	7 years (1–15)	NS	NS	NS	NS	↑ reoperation compared to auto and allograft
Ramani	1975	Retrospective	Xenograft	No	No	57	8	–	–	65	2–5 years	0 (1–2)		–	–	Adjacent vertebral body damage
Rawlinson	1994	Prospective, randomized	Xenograft	No	No	34	13	2	–	49[a]	6–18 months	19.4 (1–3)[d]			–	New neck pain
			Autograft (IC)			27	13	–	–	40[a]		71.4 (1–3)[d]			–	↑ hospital stay
Savolainen	1994	Retrospective	Xenograft	No	No	85	16	–	–	101[a]	35 months	98 (1–2)		–	–	None
			Autograft (IC)			95	54	–	–	149[a]	61 months	98 (1–2)		–	–	DSM (17%)
Siqueira	1982	Retrospective	Xenograft	No	No	161	58	2	–	221	1–8 years	100	100	100	–	None
Sutter	1995	Retrospective	Xenograft	No	No	57	9	–	–	66	1–4 years	0	0	–	–	None
Synthetic bone graft studies																
Beta tricalcium phosphate																
Dai	2008	Prospective, RCT	β-TCP	No	Yes	11	18	–	–	29	2 years	100	100	–	–	None
				Yes		14	19	–	–	33		100	100	–	–	None
Hydroxyapatite																
Bruneau	2001	Prospective	HA	Yes	No	40	14	–	–	54	24.6 months (7.4–58.2)	98	100	–	–	None
Kim	1998	Prospective	HA	No	No	67	3	–	–	70	37.1 months (1–6 years)	100	100	–	–	Graft dislocation requiring revision surgery
Senter	1989	Prospective, non-random	HA	No	No	53	27	3	1	84	6 months–3 years	NS	NS	NS	NS	Graft dislocation and fracture
			Autograft (IC)	No	No	33	31	11	–	75	4–6 years	NS	NS	NS	–	DSM (6.7%)
Suetsuna	2001	Retrospective	HA	No	No	36	–	–	–	36	4.5 years (2–7)	100	–	–	–	None
Coralline hydroxyapatite																
Agrillo	2002	Prospective	ProOsteon 200	No	Yes	33	12	–	–	45	12 months	100	100	–	–	None

Table 2 continued

First Author	Year	Design	Graft (including controls)	Plate	Cage	Number of patients according to levels operated					Specified endpoint (range)	Fusion rate (%) according to level				Significant complications related to graft
						1	2	3	4	Total		1	2	3	4	
McConnell	2003	Prospective, semi-random	ProOsteon 200	Yes	No	8	4	1	–	13[a]	24 months	78 (1–3)			–	Graft settling and fragmentation
			Autograft (IC)			10	5	1	–	16[a]		79 (1–3)			–	DSM (21.4%)
Thalgott	1999	Retrospective	ProOsteon 200	Yes	No	14	10	1	1	26	30 months (24–43)	100	100	100	100	None
Biphasic calcium phosphate																
Cho	2005	Prospective, RCT	BCP	No	Yes	15	7	28	–	50	6 months	100	100	100	–	None
			Autograft (IC)			17	13	20	–	50		100	100	100	–	DSM (6%)
Biocompatible osteoconductive polymer																
Ibanez	1998	Retrospective	BOP	No[b]	No	34	7	–	–	41[a]	12 months	18 (1–2)	–	–		Graft collapse and displacement
			Xenograft	No		32	9	–	–	41[a]		83 (1–2)	–	–		Graft collapse
Lozes	1989	Prospective[d]	BOP	No	No	107	39	6	–	150[a]	17 months (3–27)	NS	NS	NS	–	None
Madawi	1996	Prospective, semi-random	BOP	No	No	44	21	–	–	65	17.3 months (6–24)	NS	NS	–	–	Poor graft incorporation
			Autograft (IC)			38	12	–	–	50		NS	NS	–	–	Graft protrusion, intersegmental kyphosis, DSM (8%)
Polymethylmethacrylate																
Barlocher	2002	Prospective, RCT	PMMA	No	No	26	–	–	–	26[a]	12 months	0	–	–	–	None
			Autograft (IC)			30	–	–	–	30		93.3	–	–	–	DSM (17%)
			MDO			33	–	–	–	33		93.3	–	–	–	None
Boker	1989	Retrospective	PMMA	No	No	Levels not specified				83[a]	15–20 years	90				Adjacent level degeneration
Chen	2005	Prospective	Autograft	No	PMMA	63	–	–	–	63	12 months	100	–	–	–	None
Pan	2007	Prospective	Autograft	Yes	PMMA	14	7	–	–	21	19 months (13–24)	100	100	–	–	None
van den Bent	1996	Prospective, RCT	PMMA	No	No	38	4	–	–	42[a]	2 years	28 (1–2)	–	–		Graft migration
			MDO			33	6	–	–	39[a]		63 (1–2)	–	–		None

Table 2 continued

First Author	Year	Design	Graft (including controls)	Plate	Cage	Number of patients according to levels operated					Specified endpoint (range)	Fusion rate (%) according to level				Significant complications related to graft
						1	2	3	4	Total		1	2	3	4	
Factor + cell-based bone graft studies																
Bone morphogenetic proteins																
Baskin	2003	Prospective, RCT	rhBMP-2 (0.6 mg/level)	Yes	Allograft	10	8	–	–	18[a]	24 months	100	100	–	–	No symptoms, some ectopic bone formation
			Autograft (IC)			8	7	–	–	15[a]		100	100	–	–	DSM
Boayke	2005	Retrospective	rhBMP-2 (1.05–2.1 mg/level)	Yes	Yes	12	9	3	–	24[a]	13 months (12–16)	100	100	100	–	Transient symptoms, larger dose assoc with heterotopic bone formation,
Buttermann	2008	Prospective	rhBMP-2 (0.9 mg/level)	Yes	Allograft	4	16	10	–	30	2–3 years	96.7% (1–3)			–	Neck swelling
			Autograft (IC)		No	15[c]	19	2	–	36		94.4% (1–3)			–	DSM (5.6%)
Lanman	2004	Prospective	rhBMP-2 (dosage unclear)	Yes	Yes	14	4	2	–	20[a]	6 months	100	100	100	–	Severe dysphagia (5%)
Shields	2006	Retrospective	rhBMP-2 (2.1 mg/level)	Yes	Yes	61	71	6	–	151[e]	8 months	NS	NS	NS	–	Neck swelling, hematoma (9.9%)
Smucker	2006	Retrospective	rhBMP-2 (dose not standardized)	88% yes	88% Allograft	60		9		69	2 years	NS	NS	NS	NS	Neck swelling (27.5%) on av. 4.2 days postop
			Auto- or allograft	97%	No	162		3		165		NS	NS	NS	NS	None
Tumialan	2008	Retrospective	rhBMP-2 (0.7–2.1 mg/level)	Yes	Yes	96	62	36	6	200[a]	16.7 months (8–36)	100	100	100	100	Dysphagia (7%)
Vaidya	2007 (ESJ)	Retrospective	rhBMP-2 (1 mg/level)	Yes	Yes	8	9	4	–	22[g]	12 months	100	100	100	–	Neck swelling + dysphagia
			Allograft + DBM		No	11	10	3	–	24		100	90	100	–	Mild dysphagia

Table 2 continued

First Author	Year	Design	Graft (including controls)	Plate	Cage	Number of patients according to levels operated					Specified endpoint (range)	Fusion rate (%) according to level				Significant complications related to graft
						1	2	3	4	Total		1	2	3	4	
Vaidya	2007 (JBJS)	Prospective	rhBMP-2 (1 mg/level)	Yes	Allograft	Levels not specified				11	12 months	100				Graft lucency and subsidence, dysphagia (55%)
			Allograft + DBM		No					12		95.5%				None
Bone marrow aspirate																
Khoueir	2007	Retrospective	Collagen-HA matrix + BMA (~15 ml/level)	Yes	Allograft	–	22	17	27 (4–5)	66[a f]	18 months	–	96.8% (2–5)			None
Papavero	2002	Prospective	HA + BMA (0.5 ml/level after cell retention)	Yes + no	Yes	58	16	4	–	78	12 months	Increase in HA mass by 23%			–	None
Platelet rich plasma																
Feiz-Erfan	2007	Prospective, semi-random, double-blind	Allograft + PRP	Yes	No	21	29	–	–	50[a]	12 months	79 (1–2)		–	–	None
			Allograft + control blood					–	–			85 (1–2)		–	–	None

The main characteristics of the studies are listed, by graft option and the presence of control group. While radiographic results are the focus of this table, it is important to note that clinical outcomes do not necessarily correlate. 'Significant complications related to graft' lists noteworthy complications identified by the authors of this review, and by no means includes all of the complications encountered in the respective studies. As a general comparative tool, this table begins to illustrate the heterogenic and suboptimal nature of the listed papers and hence the difficulty in drawing solid conclusions

β-TCP beta tricalcium phosphate, *BCP* biphasic calcium phosphate, *DBM* dimineralised bone matrix, *DCA* dense cancellous allograft, *DSM* donor site morbidity, *F* fibula, *HA* hydroxyapatite, *IC* iliac crest, *MDO* microdiscectomy only, *NS* not specified, *PMMA* polymethylmethacrylate, *PRP* platelet rich plasma, *RCT* randomized controlled trial, *rhBMP-2* recombinant human bone morphogenetic protein-2

(4–5) = 4 and 5 level procedures included

[a] Before loss to follow-up/x-rays not available

[b] Internal fixation used for 2-level patients and one who had revision surgery

[c] 10 patients in this group did not have instrumentation

[d] Unclear

[e] Includes 13 patients who underwent vertebrectomy and fusion

[f] Includes 17 patients who underwent corpectomy and fusion

[g] Number discrepancy in the text

2. *Allograft* is somewhat substandard in comparison to autograft due to increased graft complication and reduced fusion rates, but is still an acceptable option especially when combined with plating [30].
3. *Ceramics* achieve acceptable fusion rates and clinical outcomes at a reasonable price and is thus the favourable alternative to autograft in our opinion.
4. *BMPs* are an unrefined graft technology with developing guidelines on dosage and delivery. Although BMPs demonstrate impressive osteoinductive properties, they are currently hindered by significant cost constraints and complications [23].
5. Other composite bone grafts present theoretical benefits however no consistent algorithm has been proposed. The cost of adjuvant therapies should also be taken into account.

Apart from the options discussed in this review, increasingly at the surgeon's disposal are new, although not widespread, minimally invasive techniques such as mechanical aspiration, laser-based decompression and plasma radiofrequency discectomy [18]. Most promising however are developments in cervical arthroplasty [64] and the ultimate possibilities of gene therapy [70]. However, current and emerging graft technologies must be treated with caution and a view for economic-effectiveness. Deyo et al. argue that the increasing use of new spinal fusion techniques should be scrutinised in line with evidence-based practice, with a shift in focus from how to perform them, to whom should receive them [31]. Long-term evidence, or lack thereof, for the safety and efficacy of such expensive and invasive procedures must carry significant influence on decision-making. On this note, the value of conservative management where possible is surely appreciated by the consulting surgeon.

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